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EXAMINER

IBRAHIM, MEDINA AHMED

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1638

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                                      |                                    |  |
|------------------------------|--------------------------------------|------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>09/365,349 | <b>Applicant(s)</b><br>TERRY ET AL |  |
|                              | <b>Examiner</b><br>Medina A Ibrahim  | <b>Art Unit</b><br>1638            |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 20 September 2004.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Applicant's response filed 09/20/04 in reply to the Office action of 04/20/04 has been entered. The Arisi et al (2000) reference provided after the Board decision of 07/31/03 has been considered.

The terminal disclaimer filed on 09/20/04 for claim 3 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Pat. 6, 576, 816 has been reviewed and is accepted.

Claims 1-24, pending in this application, are considered. Therefore, this Office action is made Non-Final.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 10-11, 17-18, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 10, and 11 recite "gene. ...operably linked to a heterologous promoter". A "gene" includes coding, non-coding regions, as well as all regulatory sequences associated with expression. It is unclear whether the heterologous promoter is in

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addition to the promoter already present in the gene. Dependent claims 17-18 and 24 do not obviate the rejection. It is suggested that "gene" be replaced with ---a nucleic acid---.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-8, 13-15, 19-20, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Brassica plant comprising a recombinant glutamylcyteine synthetase (ECS) expression construct and a method for decreasing heavy metal content of a medium containing an excessive amount of a heavy metal trace element by overexpressing a nucleic acid encoding glutamylcyteine synthetase in said Brassica plant, does not reasonably provide enablement for any plant including any Brassicaceae plant species which is genetically engineered to overexpress ECS for enhanced heavy metal accumulation, and a method of its use to remove heavy metal from a metal contained media. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the CAFC considered a number of factors for determining whether or not undue experimentation

would be required by one skilled in the art to make and use the invention. These factors are: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples of the invention; (d) the nature of the invention; (e) the state of the prior art; (f) the predictability or unpredictability of the art; (g) the breadth of the claims; and (h) the relative skill in the art.

The Breadth of the Claims:

Claims 1-2, 5-8, 13-15, 19-20 and 22 are broadly drawn to any plant species including taxonomically and physiologically divergent plants such as poplars, cactus, orchid, palm, corn, lettuce, tomato, chrysanthemum, rose, apple, orange, soybean, pine, lily, oat, gingko, etc, belonging to divergent species, genera, families and divisions; said any plant species genetically engineered to overexpress ECS, wherein the plant provides enhanced accumulation of heavy metal as compared with a corresponding wild-type plant. Claim 3 is broadly drawn to any plant from the family of Brassicaceae which is genetically engineered to overexpress ECS, wherein the plant provides enhanced accumulation of heavy metal as compared with a corresponding wild-type plant. The family of Brassicaceae encompasses multiple species from the genus Brassica including Brassica napus, Brassica compestris, Brassica juncea, and Brassica oleracea, The family of Brassicaceae also encompasses numerous genera other than Brassica, such as Raphanus, Arabidopsis, Crambe, Diplotaxis, Sisymbrella, Sinapsis, and Thlaspi; and multiple species within each genus, including Arabidopsis thaliana and Arabidopsis lyrata.

The Amount of Direction or Guidance Presented/The Presence or Absence of  
Working Examples:

Applicant teaches transformation of a single species of the genus Brassica, namely Brassica juncea, with the E. coli gsh1 gene, operably linked to a pea chloroplast transit sequence and to a double 35S CaMV promoter. Applicant teaches analysis of the ECS expression levels in the transgenic lines at the protein level, and growth and tolerance analysis of the transformed seedling/ mature plant (EXPERIMENTAL PROTOCOLS AND RESULTS FOR EXEMPLARY EMBODIMENTS on pages 8-10). Applicant further teaches analysis of cadmium (Cd) accumulation and tolerance, and non-protein thiol (NPTS) and glutathione content of the transformed and non-transformed Brassica juncea plants. Under Cd treatments, the ECS plants had shown significantly longer shoots and roots than wild type plants. Under control conditions there were no significant differences in root or shoot length between the ECS and the wild type plants. The ECS Brassica plants also showed improved Cd accumulation, increased levels of glutathione and non-protein thiol compounds, with no phenotypic differences as compared to untransformed plants (page 11-13).

The specification does not provide sufficient guidance for a plant other than a Brassica plant which is genetically engineered to overexpress ECS, and whereby the plant is capable of enhanced heavy metal accumulation as compared to a comparable untransformed plant. Brassica plants such as Brassica juncea are known in the art to naturally accumulate heavy metals such as cadmium, even in an untransformed state. Such plants are termed "accumulators" ( See, Salt et al. Plant Physiology ,1996, vol.

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109, pp. 1427-1433; Raskin et al. US 5,785,735; and WO 96/32016). While the ECS gene has been isolated and characterized from various organisms, neither the instant specification nor the prior art provides evidence that suggests the overexpression of this enzyme would induce heavy metal accumulation in a nonaccumulator plant.

The specification provides only prophetic guidance for a number of other plant species and their transformation with a number of ECS genes from various organisms for enhanced heavy metal accumulation.

The Nature of the Invention:

Transformation of a plant to overexpress ECS for enhanced heavy metal accumulation is complex. The mechanism of heavy metal accumulation in plants other than Brassica is yet to be elucidated. See Hofgen et al (Amino Acids (2001) 20:291-299, provided in the last Office action); Salt et al. (Plant Physiology (1996), vol. 109, pp. 1427-1433, provided in the last Office action).

State of the Prior Art/Predictability or Unpredictability of the Art:

The ability of a plant to accumulate heavy metals is genotype dependent and varies greatly between species and between cultivars within the species (Salt et al Biotechnology, vol. 13, pp. 468-474, 1995, previously provided). Noctor et al (1998, previously provided) teach that overexpression of ECS enzyme did NOT increase Cd tolerance in transgenic poplars grown in Cd contaminated soil. Goldsbrough (1999, previously provided) teaches that an overexpression of ECS gene did NOT increase the Cd tolerance of wild type Arabidopsis thaliana. The prior art does NOT establish a definitive relationship between overexpression of ECS and enhanced accumulation of

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heavy metals. For example, De Knecht et al (1992, previously provided) disclose Cd-tolerant *Silene vulgaris* plants synthesizing LESS phytochelatins than sensitive plants when exposed to the same concentration of Cadmium. Chen et al (1994, previously provided) teach that the observed cadmium tolerance in tomato cells which overproduce ECS was not stable over time, and that metal-tolerant plants exhibit inferior growth characteristics. Also, Delhaize et al (1989, previously provided) teach that relative overproduction of ECS or phytochelatins was not responsible for Cd tolerance in *Datura innoxia*. Hence, the prior art does NOT establish a predictable relationship between overexpression of ECS and enhanced accumulation of heavy metals.

Furthermore, the prior art teaches that not all plants from even the single family Brassicaceae, as claimed in claim 3, are capable of enhanced heavy metal accumulation. Peer et al. (New phytologist, 2003, vol. 159, pp.421-430, previously provided) teach the use of Brassicaceae plants from the genus of *Arabidopsis* for phytoremediation. On page 421, 1st full paragraph, Peer states "*Arabidopsis thaliana* has become a model molecular genetic system for the study of basic plant biology due to its extensive genetic characterization, compact genome, known genomic sequence, compact growth habitat, and the availability of tools for its molecular genetic manipulation. However, it does NOT accumulate metal". Thus, Peer et al support the prior teaching of Goldsbrough (1999), discussed above. Guerinot et al (Plant Physiology, 2001, vol. 125, pp. 164-167, previously provided) suggest that it is unlikely that the regulation of a single gene will be sufficient to convert non-metal accumulators



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into metal accumulators (see page 166, column 1, the last two sentences of the 1<sup>st</sup> full paragraph).

The *Brassica juncea* is known metal accumulator that has been identified as a plant useful for phytoremediation. In addition, the mechanisms of metal uptake and accumulation in *Brassica juncea* are well documented in the prior art. See, for example, Salt et al. (Plant Physiology (1996), vol. 109, pp. 1427-1433, previously provided); Raskin et al. (US 5, 785,735); and WO 96/32016, previously provided)

The Relative Skill in the Art:

The skill of those in the art, who transform plants for overexpression of an enzyme, is high, i.e., generally a PhD in molecular biology/plant physiology.

The Quantity of Experimentation Necessary:

In order for the skilled artisan to carry out the plant and method as claimed, any plant species including those from Brassicaceae family which is genetically engineered to overexpress ECS, wherein the plant provides enhanced accumulation of heavy metal as compared to a corresponding wild type plant, undue trial and error experimentation would be required. Given the limited guidance in the specification and the uncertain and unpredictable relationship between overexpression of ECS and enhanced heavy metal accumulation of the prior art, undue experimentation would be required to screen through a myriad of transgenic ECS plants from varied genera, species and cultivars; even including those from the single Brassicaceae family of claim 3, to identify those with enhanced heavy metal accumulation ability. One skilled in the art would have to proceed with trial and error experimentation to practice the full scope of the claimed

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invention in view of the lack of guidance in the specification or the prior art. One of skill in the art would not reasonably be able to extrapolate Applicant's results to any plant overexpressing ECS, particularly in view of the negative results with Brassicaceae and non-Brassicaceae plants as discussed above, absent further guidance.

Therefore, given the breadth of the claims; the lack of guidance; the limited working example; the unpredictability in the art; the state of the art; the level of skill in the art; and the nature of the invention as discussed above, the claimed invention is not enabled throughout the broad scope.

### ***Double Patenting***

Claims 4, 9-12, 16-18, 21 and 23-24 remain rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-23 of prior U.S. Patent No. 6, 576, 816. This is a double patenting rejection. This rejection is repeated for the reasons of record as set forth in the last Office action of 04/20/04. Applicant has not responded to this rejection, therefore the rejection is maintained.

The Terminal Disclaimer of 20 September 2004 obviated the obviousness-type double patenting rejection to claims 1-2, 5-8, 13-15, 19-20, and 22 as being unpatentable over claims 1-12 of U.S. Patent No. 6, 576, 816.

### ***Response to Arguments***

Applicant argues that the enablement rejection of claim 3 is improper per 37 CFR 1.198, since the same rejection was already reversed by the Board of Patent Appeals (response of 20 September 2004, page 7).

The Examiner notes that 37 CFR 1.198 permits the reopening of prosecution under the provision of 37 CFR 1.114, i.e. the filing by Applicant of a Request for Continued Examination. Such a request was indeed filed by Applicant 17 October 2003.

Furthermore, the Examiner notes that the instant enablement rejection of claim 3 is not "the same" one as that previously reversed. The enablement rejection of claim 3 presented in the Examiner's Answer of 05 July 2001 relied upon the following references: Noctor et al, Goldsbrough, De Knecht et al, Chen et al, and Delhaize et al (see pages 7-8 of the Answer). In contrast, the enablement rejection presented in the Office action of 20 April 2004 relied upon newly cited references Hofgen et al, Salt et al, Peer et al, and Guerinot et al, in addition to Goldsbrough previously relied upon (see, e.g., pages 6-7 of the Office action of 20 April 2004).

The Examiner notes that Peer et al was cited partly to clearly emphasize that the Brassicaceae family includes multiple genera in addition to Brassica, including Arabidopsis, the subject of Goldsbrough cited previously, in addition to Biscutella, Cohlearia, and Thlaspi (see, e.g., page 421, Summary; page 422, column 1). Peer et al further taught that each genus encompasses multiple species, including the species of Arabidopsis thaliana and Arabidopsis lyrata of the genus Arabidopsis (see page 422, column 1, third paragraph). Thus, the enablement rejection presented in the Office action of 20 April 2004 is clearly NOT "the same" rejection as that reversed by the Board, Applicant's assertions notwithstanding.

Applicant is directed to page 5 of the Board Decision of 31 July 2003. The Board stated that they evaluated "the scope of enablement rejection [as] to how it pertains to plant species other than Brassica", and that they ultimately affirmed the enablement rejection of "claims ... not limited to Brassica plants". Thus, the Board indicated their conclusion that plants of genera other than Brassica were not enabled.

However, there was apparently some confusion as to the difference between the genus Brassica and the family Brassicaceae; and the difference between a species, a genus, and a family in taxonomic hierarchy. The Board appeared to reverse the enablement rejection of claim 3 alone due to the misapprehension that the genus Brassica was the same as the family Brassicaceae, using the logic that since a claim drawn to a Brassica plant was allowed in a copending application, that therefore instant claim 3 drawn to the Brassicaceae family should not be subjected to the same rejection.

In order to remove the confusion, and to stress that the Brassicaceae family encompasses many more plant genera than Brassica, Peer et al was previously submitted in the last Office action. The teachings of Peer et al are supplemented by the Wikipedia excerpt submitted herewith, which teaches that the Brassicaceae family encompasses over 450 non-Brassica genera.

With respect to the newly considered Arisi et al (2000) reference, it is noted that while Arisi discloses transformed ECS Poplars and non-transformed Poplars with increased Cd accumulation in the leaves, growth was inhibited at the highest soil cadmium concentration in all plants (see at least the Summary on page 143). At the

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paragraph bridging columns 1 and 2 of page 148, the cited reference states "

[O]verexpression of either y-ECS or GS increased Cd accumulation and tolerance in Indian Mustard. In transformed poplars, enhanced tissue y-EC and GSH do NOT confer increased tolerance to Cd ...". Therefore, Arisi et al make explicit comparison between Brassica juncea having enhanced Cd accumulation and tolerance as a result of ECS overexpression and ECS Poplars with no tolerance to the Cd accumulated. It is also noted that Arisi et al (2000), Noctor et al (1998), and Arisi et al (1997), each teach that ECS Poplars which exhibited increased ECS failed either to accumulate Cd or be tolerant to high Cd growth media. The works of Arisi et al (2000), Noctor et al (1998), and Arisi et al (1997) are all from the same laboratory. Therefore, Arisi et al (2000) do not support Applicant's position. Applicant's arguments in the Appeal Briefs of 08/08/00 and 01/25/01 regarding these references support the instant scope of enablement rejection.

Furthermore, Applicant is directed to the Response of 03 February 2000, page 2, bottom paragraph, where Applicant stated that Arisi et al (1997) did not teach enhanced heavy metal accumulation in transformed poplars. The transformed plants of Arisi et al (1997) and Arisi et al (2000) are identical, i.e., ggs11 and ggs28 lines first disclosed in Arisi et al (1997), page 367, Table 1. Arisi et al (2000) teach that there was virtually no difference in cadmium accumulation between untransformed and transformed poplars (see page 145, Table 1). Thus, claims drawn to "enhanced heavy metal accumulation", i.e., claim 1 and dependents, and wherein the enhancement is at

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least 50%, i.e., (claims 8 and 15), remain non-enabled. The Examiner withdrew the art rejection over Arisi et al (1997) on the basis of Applicant's statement .

The declaration of Lewis Feldman under 37 CFR 1.132 filed 09/20/04 is insufficient to overcome the rejection to claims 1-3, 5-8, 13-15, 19-20, and 22 under 35 USC 112, 1<sup>st</sup> paragraph as set forth above because the declaration offers mere opinion evidence rather than factual evidence as to why one skilled in the art would have been able to practice any plant including any Brassicaceae overexpressing ECS and method of their use as claimed, without undue experimentation. The declaration merely repeats what has been already presented and provides no sufficient facts to overcome the rejection. In *In re Chilowsky*, 306 F.2d 908, 134 USPQ 515 (CCPA 1962), the court stated "expert opinion that an application meets the requirements of 35 USC 112, 1<sup>st</sup> paragraph is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 USC 112, 1<sup>st</sup> paragraphs are entitled to some weight". Applicant has not provided a clear and convincing evidence that shows all plants, including those from Brassicaceae family, overexpressing ECS would provide enhanced accumulation of heavy metals from metal containing media as compared to corresponding untransformed plants. When all of the evidence is considered, the totality of the rebuttal evidence of enabling disclosure that is commensurate in scope of the claims fails to outweigh the Examiner's evidence that the enabling disclosure is not commensurate in scope of the claims. Therefore, the declaration is not persuasive and the rejection is maintained.

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**Remarks**

The claims are deemed free of the prior art because the prior art does not teach or fairly suggest a plant that is genetically engineered to everexpress glutamylcysteine synthetase (ECS) for enhanced heavy metal accumulation, nor does the prior art teach a method that employs said plant for heavy metal removal from a metal containing media.

No claim is allowed.

**Contact Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571) 272-0797. The Examiner can normally be reached Monday -Thursday from 8:00AM to 5:30PM and every other Friday from 9:00AM to 5:00 PM. Before and after final responses should be directed to fax nos. (703) 872-9306 and (703) 872-9307, respectively.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Amy Nelson, can be reached at (571) 272-0804.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12/8/04

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